Inflammopharmacology (2023) 31:57–75
https://doi.org/10.1007/s10787-022-01077-w

Inflammopharmacology

REVIEW

Statins block mammalian target of rapamycin pathway: a possible novel therapeutic strategy for inflammatory, malignant and neurodegenerative diseases

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Received: 3 February 2022 / Accepted: 12 July 2022 / Published online: 27 December 2022

Abstract

Inflammation plays a critical role in several diseases such as cancer, gastric, heart and nervous system diseases. Data suggest that the activation of mammalian target of rapamycin (mTOR) pathway in epithelial cells leads to inflammation. Statins, the inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), seem to be able to inhibit the mTOR. Statins are considered to have favorable effects on inflammatory diseases by reducing the complications caused by inflammation and by regulating the inflammatory process and cytokines secretion. This critical review collected data on this topic from clinical, in vivo and in vitro studies published between 1998 and June 2022 in English from databases including PubMed, Google Scholar, Scopus, and Cochrane libraries.

Keywords Statins · Mammalian target of rapamycin · Inflammatory diseases · Inflammation · Oxidative stress

Abbreviations

mTOR	Mammalian target of rapamycin
IBD	Inflammatory bowel diseases
CD	Crohn's disease
UC	Ulcerative colitis
IL	Interleukin
IFN-γ	Interferon gamma
PIKK	Phosphatidylinositol3-kinase-related kinase
TSc	Tuberous sclerosis complex
AKT	Protein kinase B
GTP	Guanosine triphosphate
Rags	Ras-related GTPases
GEF	Guanine exchange factor
PAT	Proton-assisted amino acid transporter

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LKB	Liver kinase B
AMPK	AMP-activated protein kinase
AXIN	Axis inhibition protein
LRS	Leucyl-tRNA synthetase
GAP	GTPase activating proteins
FLCN	Folliculin
EIF4E	Eukaryotic translation initiation factor 4E
S6K1	S6 kinase 1
mSIN1	Mammalian stress-activated protein kinase interacting protein 1
TGF	Transforming growth factor
IPF	Idiopathic pulmonary fibrosis
Grb10	Growth factor receptor-bound protein 10
ERK	Extracellular signal-regulated kinase
RSK1	Ribosomal S6 kinase 1
IKKβ	IκB kinase β
GSK3β	Glycogen synthase kinase 3β
IRS	Insulin receptor substrate
DDIT4	DNA-damage-inducible transcript 4
TP53	Tumor suppressor protein 53
ISCs	Intestinal stem cells
cADPR	Cyclic ADP ribose
SIRT1	Sirtuin 1
PTEN	Phosphatase and tensin homolog
TNFα	Tumor necrosis factor α
TRAF6	Tumor necrosis factor receptor-associated factor 6
TLR4	Toll-like receptor 4
Nod2	Nucleotide-binding oligomerization domain 2
MDP	Muramyl dipeptide
FCS	Fetal calf serum
ECH	Echinacoside
STAT3	Signal transducer and activator of transcription 3
iNOS	Inducible nitric oxide synthase
ASII	Astragaloside II
NF-κB	Nuclear factor κB

Introduction

Inflammation and oxidative stress play pivotal roles in pathogenesis of many diseases. The inflammatory mediators such as interleukins (ILs), interferons (INF-s), and tumor necrosis factor (TNF)-α can exacerbate inflammatory diseases because of overexpression of several pathways such as nuclear factor kappa B (NF-κB), peroxisome proliferator-activated receptors (PPAR-γ), signal transducer of activators of transcription (STAT), nod-like receptor family protein 3 (NLRP), toll-like receptors (TLR), mitogen-activated protein kinase (MAPK), and mammalian target of rapamycin (mTOR) pathways (Lashgari et al. 2022). Inflammation is an early trigger in many diseases including cancer, type 2 diabetes, cardiovascular disease, atherosclerosis, neurodegenerative diseases, and inflammatory bowel disease (IBD) (Lashgari et al. 2022; Lashgari et al. 2020; Roudsari et al. 2020; Zandi et al. 2021). Statins are the drugs of choice in prevention of cardiovascular disease, both in terms of efficiently lowering plasma low-density lipoproteins cholesterol (LDL-C), and in terms of cost-effectiveness. Besides their LDL-C lowering properties, statins have different pleiotropic effects such as anti-inflammatory and immunomodulatory effects, which are beneficial in management of inflammatory disorders (Pickering 2021; Glass et al. 2010; Bahrami et al. 2020; Dehnavi et al. 2021; Khalifeh et al. 2021; Shakour et al. 2020; Sohrevardi et al. 2021; Vahedian-Azimi et al. 2021; Kouhpeikar et al. 2020; Serban et al. 2015; Sahebkar et al. 2015; Bland et al. 2022).

Advanced molecular and cellular analyses showed that the mTOR pathway is involved in inflammatory process and inflammatory diseases, mainly by having effects on inflammatory mediators. The aim of this article is to present data on the inhibitory effect of statins on mTOR pathway, structures and functions, and their possible interactions which might be used as novel therapeutic approach in treatment of inflammatory diseases (Fig. 1) (Murata 2018; Kotas and Medzhitov 2015).

Mammalian target of rapamycin (mTOR) structure

mTOR refers to Tor1 and Tor2 in *Saccharomyces cerevisiae*, which are resistant to rapamycin. mTOR is a serine/threonine protein kinase which is associated with phosphatidylinositol 3-kinase-related kinase (PIKK). mTORs are involved in autophagy, protein synthesis, cell growth, proliferation, mitochondrial digestion system, and digestion systems in general. mTOR is divided into mTORC1 and mTORC2. mTORC1 consists of SEC13 protein 8 (mLST8)/G-protein β subunit-like protein (GβL), the regulatory-associated protein of mTOR (Raptor), DEPTOR, PRAS40, and platform protein TTI1/TEL2 complex (Yang et al. 2013). mTORC1 is involved in different pathways and processes such as cell development and apoptosis, DNA dysfunction, hypoxia, and regulation of autophagy. The AKT, extracellular signal-regulated kinase (ERK), and IκB kinase β (IKKβ) can all phosphorylate TSC, resulting in activation of mTORC1. mTORC2 is composed of mTOR and the mammalian stress-activated protein kinase association protein 1 (mSIN1), mLST8/G_L, drug-insensitive companion of mTOR (DICTOR), Protor 1/2, DEPTOR, TTI1, and TEL2 (Yang et al. 2018). The TSC family is responsible for regulation of the mTOR pathway. AMPK phosphorylates TSC2 and mTORC1. mTORC1 regulates the cell hemostasis and inflammation, while mTORC2 controls cell survival and proliferation. mTOR pathway is also controlled by the

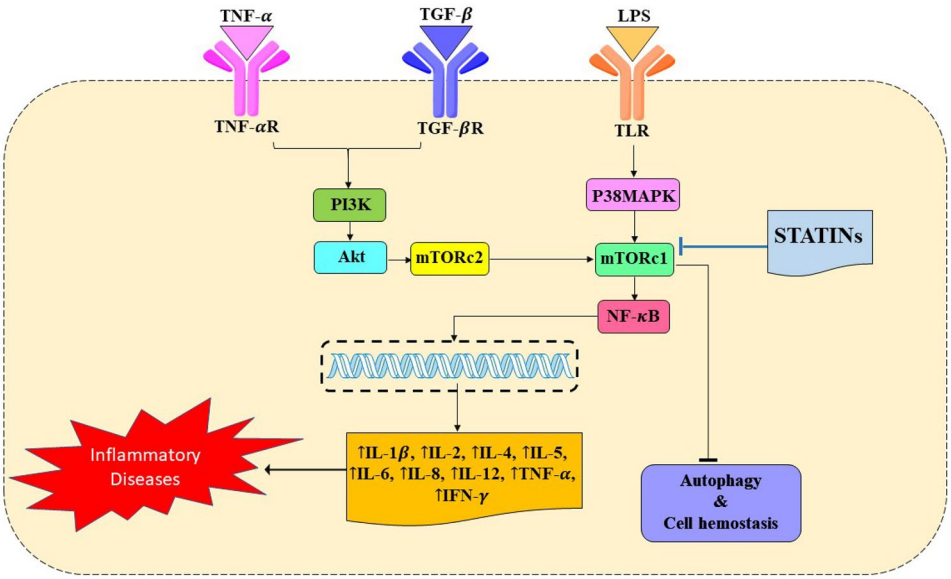

Fig. 1 Role of statins in modulation of inflammatory diseases

PI3K/AKT signals. PI3K stimulates mTORC2 and mTORC1 (Kaur et al. 2021; Afify et al. 2021).

mTOR and inflammatory mechanisms

As mentioned, mTOR signaling pathway mediates the inflammatory reactions and inflammatory diseases (Fig. 1). Inactivation of the mTOR signaling leads to autophagy. Autophagy contributes to the modulation of cell processes. Rapamycin, as the mTOR inhibitor, can initiate autophagy. It was demonstrated that mTOR signaling pathways and their overlaping with other inflammatory pathways may activate the inflammatory cascade and could be considered as a novel therapeutic approach for inflammatory diseases (Lee and Hung 2007; Dazert and Hall 2011).

It was well established that oxidative stress and free radicals trigger the inflammatory reactions due to DNA damage, resulting in secretion of tumor necrosis factor α (TNFα), IL-1β, TGF-β, IL-12, and IL-6. TGF-β induces the P13/AKT signaling pathway leading to the mTORC1 activation. In addition, TGF-β directly enhances the mTORC1 activation and contributes to the modulation of inflammatory process. It was shown that statins could inhibit mTORC1. The phosphorylated AKT (p-Akt) activates mTORC1, resulting in inhibition of autophagy. Suppression of the PI3K-AKT signaling pathway decreases the inflammatory response and stimulates autophagy, leading to modulation of the inflammatory reactions (Gagliano et al. 2013; Tiedemann et al. 2017). PTEN and PI3K-AKT can be inhibited by several drugs, among which statins are quite important, mainly by downregulation of mTORC1 expression and induction of autophagy. This effect offers a possibly important pathway for management of inflammation. Inhibition of PI3K-AKT-mTORC1 suppresses the IKK/NF-kB signaling and can block the production of IFN-γ, IL-6, IL-8, IL-1, and TNF-α (Torrealba et al. 2019; Dan et al. 2008). TLR4 activates mTORC1 by both P13/AKT and p38MAPK signaling pathways. Phosphorylation of mTORC1 induces TGF-β, AKT, and P38MAPK. Therefore, the mTORC1 pathway can be a basic trigger for inflammatory events. It has been shown that prevention of mTORC1 by statins can switch the P38MAPK/mTORC1 activity, proposing a probable approach for designing drugs with anti-inflammatory and therefore beneficial effects on inflammatory diseases (Hernández et al. 2011; Pazhooh et al. 2021).

Statins

Among a myriad of new and classical lipid-lowering agents (Sahebkar and Watts 2013a; Sahebkar and Watts 2013b; Backes and Hilleman 2021), statins are the first choice for atherosclerotic cardiovascular disease (CVD) prevention. Statins decrease serum LDL-C by inhibiting the enzyme HMG-CoA reductase, which is crucial for the synthesis of L-mevalonate—a precursor of cholesterol. Therefore, they reduce cholesterol production in the cells, particularly hepatocytes, and decrease metabolites of the cholesterol synthesis cascade, including isoprenoid compounds such as farnesyl pyrophosphate (FPP), and geranyl phosphatidylcholine (GGPP). GTP-binding proteins are affected and have effects on cells' shape, secretion, differentiation, motility, and proliferation. Statins are either based on some natural substances such as lovastatin, mevastatin, pravastatin, pitavastatin, and simvastatin, which are fungal derivatives or are totally synthetic such as atorvastatin, fluvastatin and rosuvastatin. These drugs can be differentiated based on their differences in lipophilicity/hydrophilicity, elimination half-life,

and effects on decreasing LDL-C. Statins are known to be safe. However, their tolerance remains a clinically important issue affecting long-term compliance (Pinal-Fernandez et al. 2018; Jain and Ridker 2005; Banach et al. 2015).

The mTOR/statins intervention in different inflammatory diseases

Malignant diseases

According to some earlier studies, the activity of the mTOR signaling increases in different malignant diseases. It was estimated that the mTOR signaling has an effect on approximately 30% of solid malignant diseases and its dysregulation is considered to be one of the most fundamental mechanisms involved in pathophysiology of solid malignant tumors (Fruman and Rommel 2014). Several mechanisms are implicated in this effect. First, since mTOR participates in several cell biology processes including cell proliferation, growth and survival, there is no doubt that mTOR is involved in malignant processes (Mayer and Arteaga 2016). Second, in human malignant diseases, several mutations were observed in different elements of the PI3K signaling pathway, which were upstream of mTORC1 and mTORC2. Third, it has been shown that several genes such as serine threonine kinase 11, PTEN, Tsc1/2, and neurofibromatosis type1, were mutated in some familial malignant syndromes, and were located upstream of the mTOR signaling pathway (Laplante and Sabatini 2012). Moreover, p53 loss, a common event in different malignant diseases, can activate mTORC1 (Feng et al. 2005). As already mentioned, the mTOR signaling is involved in cell proliferation and metabolism, thereby participating in tumorigenesis and tumor progression. It has been shown that dysregulation in protein synthesis at the 4E-BP1/eIF4E level, which is a downstream of mTORC1, plays a crucial role in tumorigenesis (Dowling et al. 2010). The eIF4E mRNAs, expressing pro-oncogenic proteins, mediate tumor angiogenesis, progression, and metastasis (Hsieh et al. 2010). There is a plethora of evidence indicating that the mTOR activation correlates with the enhancement of the biogenesis of ribosome, which stimulates cell proliferation, and consequently enhances the cell growth (Laplante and Sabatini 2012). mTOR can also stimulate cell growth by inhibiting the autophagy process (White 2015). Since autophagy is considered to be anti-tumorigenic, inhibition of autophagy results in tumor formation. Recent evidence suggests that under specific situations, autophagy may unexpectedly contribute to tumor progression (Iacobuzio-Donahue and Herman 2014; Rosenfeldt et al. 2013; White and DiPaola 2009). mTORC1 inactivates the UNC-5-like autophagy-activating kinase 1 (ULK1), thus preventing the formation of ULK1-ATG13-FIP200 complex, an essential factor for autophagy initiation. Besides mTORC1, mTORC2 has the potential to block autophagy by activating mTORC1 (Hosokawa et al. 2009; Jung et al. 2009; Kim and Guan 2015). Many attempts have been made to evaluate the anti-tumor effects of statins as monotherapy or in combination with chemotherapeutics (Gazzerro et al. 2012), and it seems that statins are efficient in suppressing different types of malignant tumors including oesophageal, lung, liver, breast, pancreatic, endometrial and colorectal tumors (Hassanabad 2019).

Renal cell carcinoma (RCC)

Although the incidence of renal cell carcinoma RCC has an increasing trend in both genders around the world, this trend is stable in most developed counties. However, in low- and middle-income countries, RCC incidence has an increasing trend (Znaor et al. 2015). Surgical treatment is the first option for localized RCC. However, in aggressive tumors it should be combined with other treatments with drugs like sorafenib (Escudier et al. 2007) and temsirolimus (Miyake et al. 2013), which act due to their effects on the receptor tyrosine kinases and mTOR signaling pathways. The use of these drugs is associated with several problems including adverse effects and high cost (Thompson-Coon et al. 2010). Therefore, there is an urgent need for drugs which would prolong the patients' survival with low cost and limited adverse effects. It was shown that cell metabolism is significantly altered in RCC, and mTOR is a potent mediator of cell metabolism (Linehan et al. 2010). The Cancer Genome Atlas reported that genetic mutations in the PI3K/AKT/ mTOR signaling pathway were detected in 6% of RCC patients (Grabiner et al. 2014). A comprehensive genomic profiling in patients with advanced papillary RCC showed genomic mutations of PI3K/mTOR in 8% of cases (Pal et al. 2018). In chromophobe RCC, genetic mutations in genes associated with the mTOR pathway appeared in 15% (23 out of 66) cases (Davis et al. 2014).

Head and neck squamous cell carcinoma (HNSCC)

Head and neck carcinoma is the sixth most common type of cancers, accounting for about 3% of all cancers (Jemal et al. 2011). High morbidity and mortality make it one of the most dangerous cancers (Rose et al. 2011). Despite all efforts in developing the treatment strategies for head and neck carcinoma such as surgery, chemotherapy, and radiotherapy, unfortunately the outcomes are unsatisfactory (Bernier et al. 2009). A whole-exome sequencing study showed that about 30% of HNSCC patients had mutations in the PI3K pathway (Lui et al. 2013). It was shown that the mTOR signaling is activated in approximately 80–90% of HNSCC patients, particularly in those with positive HPV infection (Molinolo

et al. 2007). Patients with advanced HNSCC have a number of mutations including PIK3CA, mTOR, and PTEN indicating that the co-existence of these mutations could be associated with progression of the disease (Giudice and Squarize 2013).

Endometrial cancer (EC)

EC is the most prevalent gynaecological cancer in developed countries, mainly due to an increase in epidemic of obesity, so globally as well (Morice et al. 2016). Satisfactory outcomes are expected in patients who are diagnosed with early stages of EC. However, in patients with advanced EC current treatment options including surgery, chemotherapy, and radiotherapy are not very successful (Saso et al. 2011). Therefore, there is a need for new drugs to treat patients with advanced EC.

Lymphangioleiomyomatosis (LAM)

LAM is a rare progressive lung disease, mostly affecting females in reproductive age. It is associated with mutations in tuberous sclerosis (TS) genes, renal angiomyolipomas, and lymphatic spreads (McCormack 2008). Studies on tuberous sclerosis complex (TSC) 1 and 2, the negative regulators of mTOR, provided a new insight into the LAM pathophysiology and enabled development of new drugs including sirolimus for the treatment of LAM (Goncharova et al. 2002; Kwiatkowski et al. 2002). Promising results have been achieved with sirolimus in clinical settings. Concerning lungs, it was shown that following treatment with sirolimus the mean forced expiratory volume in 1 s (FEV1) and the forced vital capacity (FVC) increased, and the residual volume decreased when compared with baseline values. (Bissler et al. 2008; Davies et al. 2011). Besides, sirolimus induced regression of kidney angiomyolipomas, SEGAs, and liver angiomyolipomas in LAM patients (Dabora et al. 2011).

Breast cancer (BC)

BC is the most prevalent malignancy in women, involving one in eight of US women. Several risk factors have been suggested for BC such as obesity, family history, hormone replacement therapy, and genetic defects (Islam et al. 2017). Obesity does not only increase the BC incidence, but also worsens the prognosis of the disease as well. Dyslipidemia, including hypercholesterolemia, is a frequent comorbidity of obesity (Borgquist et al. 2018). Lowering plasma cholesterol level maight be beneficial in management of BC patients. The majority of genetic alterations in BC are located upstream of the mTOR pathway, contributing to the hyperactivation of the mTOR signaling. Mutations in PIK3CA are common in BC patients and nearly 20–50% of cases have them. These mutations participate in 35%, 23%, and 10% of hormone-receptor positive, human epidermal growth factor receptor 2-positive, and triple-negative BCs, respectively (Stemke-Hale et al. 2008). Mutations in PTEN appear in 3% of BC patients, while PTEN loss can be detected in about 30% of BC patients (Stemke-Hale et al. 2008; Engelman et al. 2006). The mTOR mutations also occur in BC patients and are mostly located at FAT and FATC domains (Hardt et al. 2011).

Prostatic cancer (PC)

PC is the most prevalent type of cancer in men throughout the world, and is considered as the second leading cancer-related death cause in the US (Bashir 2015; Roudsari et al. 2021). Despite significant improvements in treatment strategies for PC, the advanced disease is associated with relatively high mortality (Sartor and Bono 2018). Therefore, it is important to develop new drugs to treat PC. The mTOR pathway was found to be significantly activated in PC and genetic alterations in the mTOR signaling were found in 42% of PC tissues (Taylor et al. 2010). Genetic mutations in the PI3K/Akt signaling pathway were detected in 30–50% of primary PC tissues (Morgan et al. 2009).

Glioblastoma (GBM)

GBM is the most prevalent brain tumor in adults with the highest death rate among all brain tumors (Ostrom et al. 2018). The current strategies for GBM treatment include surgery, chemotherapy, and radiation. Nevertheless, the patients have poor outcomes with the median survival time of approximately 14 months. Unfortunately, the GBM progression is unavoidable, thus making it one of the most lethal malignant tumors (Meir et al. 2010).

Colorectal cancer (CRC)

CRC is considered as a major global health problem with an increasing incidence rate worldwide (Arnold et al. 2017). Although there are remarkable advancements in CRC treatments, the outcomes of patients with advanced CRC are still quite poor. The major focus today is on improvement of prevention strategies (Segnan et al. 2005). A relatively recent meta-analysis indicated a lower incidence rate of CRC following statin treatment (Bonovas et al. 2007). Another study suggested that statins have a beneficial effect on CRC cells by activating the bone morphogenic protein (BMP) (Kodach et al. 2007).

Myotoxicity/myopathy

Statin therapy may be accompanied by some adverse effects, especially musculoskeletal (Ward et al. 2019). Statin-related muscle symptoms vary from mild muscle fatigue to rhabdomyolysis characterized by massive damage of muscles, resulting in release of intracellular muscle cells contents into the bloodstream (Simic and Reiner 2015; Reiner 2014). Although a plethora of evidence supports the idea that high doses of statins may cause higher risk of statin-related myopathy, the mechanisms that contribute to muscle damage remain poorly defined. For instance, impairment in mitochondrial activity (Kaufmann et al. 2006); overexpression of atrogin-1, which can act as a mediator of muscle injury in patients treated with statins (Hanai et al. 2007); decrease in synthesis of muscle proteins subsequent to the suppression of eIF2B expression (Tuckow et al. 2011); suppression of Rab1 GTPase that causes endoplasmic reticulum–to-Golgi traffic inhabitation (Sakamoto et al. 2011); and reduction in creatine synthesis have been implicated in statin-induced myopathy (Mangravite et al. 2013).

It was also suggested that the AKT signalling pathway plays an important role in statin-related myopathy (Mullen et al. 2011). In muscle cells, AKT is activated by several factors including hormones, cytokines, and growth factors, which induce the AKT transmission to the plasma membrane and therefore AKT phosphorylation. The AKT pathway induces protein synthesis and degradation by activation of mTOR (Schiaffino and Mammucari 2011), and forkhead box O inhabitation (Crossland et al. 2008). Thus, the AKT pathway plays an important role in muscle growth. AKT activates the mTOR pathway by two different mechanisms that induce protein synthesis. First, mTOR induces the phosphorylation of the ribosomal protein S6 kinase (rpS6), and as a result activation of the rpS6 occurs (Magnuson et al. 2012). Second, mTOR makes eIF4E accessible for protein synthesis by phosphorylating the 4E-BP1, leading to interruption of 4E-BP1 interaction with eIF4E (Gingras et al. 1998). The mTOR signalling pathway may be involved in statin-related myopathy. Statins change the AKT phosphorylation at S473 level unlike T308. mTORC2 phosphorylates the AKT at S473 level. Furthermore, statins inhibit the effects of mTORC1 on dysregulation of rpS6, s6K, and 4E-BP1 phosphorylation. Therefore, impairment in the AKT/mTOR signalling pathway may be the key mechanism for the statin-related myopathy (Bonifacio et al. 2015; Bouitbir et al. 2020).

Wound healing

The burns and injuries are considered to be an important health problem globally (Stylianou et al. 2015). There are three categories of burns based on the severity of the injury including the first-degree or superficial, second-degree involving partial thickness of the skin, and third-degree involving full-thickness of the skin (Ocon et al. 2019). Several complications may occur following burns such as infections, hypertrophic scars, as well as mental and functional disabilities (Deeter et al. 2019). It has been suggested that procrastination in wound-healing correlates with significantly higher mortality (Nitzschke et al. 2014). Significant efforts have been made to develop therapeutic options to accelerate the process of wound healing (Zhao et al. 2019). This process is stratified into four main stages; (1) hemostasis, (2) inflammation, (3) proliferation, and (4) resolution (Gosain and DiPietro 2004).

The Akt/mTOR pathway has been involved in different stages of wound-healing process including extracellular matrix (ECM) remodelling (Zhang et al. 2006), re-epithelisation (Calautti et al. 2005; Kitamura et al. 2008), and collagen production (Blakytny and Jude 2006; Ong et al. 2007). Several studies tried to find out how regulation of the AKT/mTOR pathway may affect wound-healing (Huang et al. 2015; Xing et al. 2015). Stimulation of the AKT/mTOR pathway increased cell proliferation, migration, and wound healing (Squarize et al. 2010). Castilho et al. claimed that overexpression of the AKT/mTOR pathway accelerated the proliferation and migration of epithelial cells and, consequently, the wound healing process (Castilho et al. 2013). Later, it was shown that the activation of AKT/mTOR facilitates the wound-healing process by enhancing angiogenesis and fibrogenesis (Tomioka et al. 2014).

Diabetic ulcers

Slower wound healing is a well-known complication associated with diabetes mellitus and is attributed to higher apoptosis rate, and decrease in angiogenesis, collagen formation and organization as well as infiltration delay (Fadini et al. 2010; Jeffcoate and Harding 2003; Lerman et al. 2003). Lymphatic vessels are known to be important for draining proteins from the extracellular area and tissues around the wounds, and also for adjusting the immune system responses (Oliver and Detmar 2002; Witte et al. 2001). Impairment of lymphatic vessels function could result in refractory diabetic wounds (Saaristo et al. 2006). It has been shown that the mTOR pathway stimulated the accumulation of myeloid-derived suppressor cells (MDSCs). In high-glucose environments, MDSCs is differentiated into inflammatory macrophages, which have the ability to impair the process of diabetic ulcers healing. Therefore, blocking of mTOR could contribute to improvement of diabetic-ulcer healing process (Li et al. 2021).

Depression

Depression, a very common psychiatric state and is one of the major causes of disability worldwide. It is a syndrome characterized by, but not limited to, repeated episodes of low mood, feeling guilt and worthlessness, problems with sleep and appetite as well as libido (James et al. 2018). Every individual is at 17% risk of developing major depressive disorder during his/her lifetime (Kessler et al. 2005). Although the treatment options for depression have evolved during the time, the effects of new anti-depressant drugs are still very far from desired (Rush et al. 2006). For example, in a clinical trial on patients diagnosed with major depression, the response rate in placebo group was 35–40%, while the response rate of patients treated with anti-depressants was 50–60% (Furukawa et al. 2016). Therefore, there is an urgent need for new anti-depressants. Recent studies have focused on finding drugs that target alternative pathways causing depression (Cowen 2017). Several mechanisms were investigated in animal models such as an increase of serotonergic effects (Al-Asmari et al. 2017), change in blood cortisol concentration and hippocampus concentration of serotonin (ElBatsh 2015), inhibition of NMDA receptors and NO-cGMP synthesis (Ludka et al. 2013), as well as an increase of the brain-derived neurotrophic factors (Ludka et al. 2013; Ludka et al. 2017). Statins can reduce depressive-like behaviour by decreasing neuronal apoptosis, microglia, and oxidative stress, as well as by suppression of TNF-α, IL-1, and IL-6 expression (Lim et al. 2017; Taniguti et al. 2019; Yu et al. 2019). Only one study demonstrated that the mTOR signalling pathway may be responsible for antidepressant-like effects of statins (Ludka et al. 2016).

Amyotrophic lateral sclerosis (ALS)

ALS is a detrimental neurodegenerative disease affecting both the upper and lower motor neurons (Pratt et al. 2012). The aetiology of ALS has not been clarified so far and no particular treatment has been found. ALS is associated with muscle atrophy, fibrosis, and inflammation (Iwasaki et al. 1991; Jensen et al. 2016). The mTOR signalling is important for muscle regeneration by regulating the myogenic gene expression (Lepper et al. 2009). An in vivo study showed that the AKT/mTOR activation induced muscle hypertrophy and prevented muscle atrophy (Bodine et al. 2001).

Parkinson disease (PD)

PD is the second most prevalent neurodegenerative disorder affecting 2–3% of individuals older than 65 years (Poewe et al. 2017). The main current strategy for management of PD is symptomatic treatment with drugs that increase the dopamine levels (Connolly and Lang 2014; Lashgari et al. 2021). Although the current treatments increase the patients' quality of life, they are not able to prevent the progression of the disease (Kalia et al. 2015). Autophagy is one of the central mechanisms involved in pathogenesis of PD and some studies suggested that increase in autophagy might have neuroprotective properties (Park et al. 2014; Tan et al. 2014). Statins are able to activate autophagy by inducing the AMPK and mTOR pathways. Therefore, there is a possibility that statins might have the potential to be beneficial for patients with PD (Lashgari et al. 2021).

COVID-19

Recently, the world is facing serious consequences of pandemic of the a new disease, COVID-19, caused by SARS-CoV-2 (Khatami et al. 2020). The speed of COVID-19 spread and its high mortality caused a great interest in studying all the aspects of this disease during the past two and half years. The efficacy of many agents/drugs for COVID-19 treatment has been evaluated. However, no specific treatment was fully efficient so far. To develop new drugs/agents against COVID-19, it is important to identify the virus structure (as well as those of all variants), life cycle, and the disease process. The mTOR downstream signalling pathways play an important role in a variety of cellular functions including protein synthesis, metabolism, autophagy, cell cycle, and regulation of the immune system (Laplante and Sabatini 2012). The mTOR distribution contributes to several disorders such as CVD, cancer, and some metabolic diseases (Saxton and Sabatini 2017; Weichhart 2018). It was found that a cross-talk between the virus and the AKT/mTOR pathway may cause a significant decrease in production of the virus (Appelberg et al. 2020). An in vitro study indicated that the PI3K/Akt/mTOR pathway might be a key pathway in COVID-19 infection. The effects of three mTOR inhibitors on SARS-CoV-2 were assessed and it was found that the PI3K/Akt/mTOR, DNA-damage response pathway, and ABL-BCR/MAPK are essential for the virus infection (Garcia et al. 2020). Altogether, the mTOR signalling pathway is crucial for the virus infection, replication, and progress by inducing autophagy, prevention of protein synthesis, and suppression of inflammation (Khan 2021). Therefore, targeting the mTOR signalling pathway could be an interesting objective for treatment of SARS-CoV-2 infection (Khan et al. 2021).

It was hypothesized that statins have several properties which may be useful in SARS-CoV-2 treatment including: (1) suppression of the CD147 expression, which is crucial for the virus entry and human cells infection; (2) modification of lipid rafts caused by the virus causing a decrease of infection and viral replication; (3) modification of autophagy which is probably involved in SARS-CoV-2 infection; (4) suppression of the virus induced uncontrolled inflammation

which has deleterious effects on patients health; and (5) decrease in thrombus formation that is considered as one of the most often complications of COVID-19 (Rodrigues-Diez et al. 2020). Therefore, several clinical studies have been performed to assess the effects of statins on COVID-19. A recent meta-analysis confirmed the beneficial effects of statins on clinical outcomes of patients with COVID-19 and encouraged patients who are on statin treatment to continue the drug treatment during COVID-19 infection (Pal et al. 2021).

Statins in treatment of inflammatory diseases: targeting the mTOR pathway

Many studies have been performed with the aim to understand the role of statins in inhibition of inflammatory process (Fig. 1). This review highlighted the potential of statins in treatment of inflammatory diseases. The effects of different statins are discussed below.

Atorvastatin

Statins decrease serum LDL-C and therefore can prevent CVD (Table 1) (Han et al. 2018). 3MA or LY294002 is a suppressive inhibitor of atorvastatin by phosphorylation of AMPK, AKT, and mTOR in LPS-induced IL-1β and TNFα expression in RAW264.7 (Table 1) (Ludka et al. 2013). Compound C, an AMPK inhibitor, was shown to control autophagy by atorvastatin through AMPK/mTOR in vitro and in vivo (Sheng et al. 2020). Atorvastatin induced cellular autophagy in cervical cancer cells, which was confirmed by upregulation of the AMPK, and AKT/mTOR pathways. Combination of atorvastatin and the autophagy inhibitors might be a new option for cervical cancer treatment (Jones et al. 2017). A plethora of evidence has shown that statins have anti-inflammatory effects in patients with ankylosing spondylitis (AS). Atorvastatin can also suppress the expression of IL-1β, and TNFα in murine macrophages (Table 2) (Jin et al. 2012). IFN-γ, TNF-α, IL-1, IL-2, IL-6, and TGF-β block the arrangement of autophagosomes, while IL-4, IL-10, and IL-13 induce autophagy. Autophagy reduces the release of IL-1β by inhibition of NLRP3 inflammation. The autophagosome arrangement suppresses the p38MAPK phosphorylation, which occurs in down-regulation of TNF-α (Qu et al. 2013). Ludka et al. suggested that atorvastatin improved depression by the PI3K/Akt/GSK-3β/mTOR pathway. Atorvastatin activated AKT/mTOR, while it inhibited the GSK-3β. Therefore, it was suggested that, at least this statin, might have a favourable antidepressant-like effect.

Simvastatin

Simvastatin decreased the expression of AKT, and mTOR in A498 and 786-O renal cancer cells (Table 2). Simvastatin seems to have anti-tumor effects by suppressing the IL-6-induced phosphorylation of mTOR/JAK2/STAT3. It has been demonstrated that simvastatin has anticancer properties due to inhibition of the mTOR/AKT pathway (Markowitsch et al. 2020). Rapamycin (a mTOR inhibitor) decreased olanzapine (OLZ)-stimulated hepatocellular lipids content in HepG2 cells (Table 2). It was shown that simvastatin improves OLZ-induced lipid metabolic content by inhibition of the mTOR signaling pathway (Liu et al. 2019).

Topical application of simvastatin increased collagen production, and enhanced the myofibroblast population in male Wistar rats. Therefore, it might be recommended for wound healing (Table 1) (Ramhormozi et al. 2021). The analysis of qRT-PCR showed improved wounds healing as a result of simvastatin treatment due to inhibition of AKT/mTOR and the effects of simvastatin on inflammatory process (Rezvanian et al. 2021). Simvastatin suppressed endometrial cancer cells (ECC) proliferation in a dose dependent way due to inhibition of the AKT/mTOR pathway in ECC and Ishikawa cells (Table 2) (Stine et al. 2014). RCC is often resistant to chemotherapy and radiation. Simvastatin suppressed cell development of A498 and 786-O cells (Table 2). Simvastatin suppressed RCC cells apoptosis by inhibition of AKT/mTOR,/ERK (Fang et al. 2013). Simvastatin also had anti-tumor effects in breast cancer. In clinical studies, simvastatin blocked the PI3K/Akt/mTOR signaling by inducing PTEN and by dephosphorylating AKT and S6RP (Wang et al. 2016).

A recently published study showed that treatment with simvastatin was associated with inhibition of proliferation, migration, and tumorspheres-formation in PCa cells (Jiménez-Vacas et al. 2021). Simvastatin was found to be beneficial in diabetic ulcers. In diabetic mice, simvastatin upregulated the VEGF mRNA expression and the content of nitric oxide in a wound, reduced the H2O2-induced apoptosis, and increased the infiltration of M2 macrophages, thereby improving the wound-healing process. VEGF was the main factor responsible for restoring wound healing in diabetic ulcers treated with simvastatin Bitto et al. 2008). Topical application of simvastatin was associated with acceleration of diabetic ulcer healing, at least partially, by the AKT/mTOR signalling pathway (Asai et al. 2012).

Lovastatin

Lovastatin was shown to decrease the levels of nitric oxide by decreasing inducible nitric oxide synthase (iNOS) expression in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells (Table 2). The mRNA level of TNF-α

Table 1 Clinical and in vivo studies on mTOR/statins interaction in inflammatory diseases

Study design	Disease	Intervention		Number of Patients		Treatment Duration	Results	Refs.
		Case	Control	Case	Control			
Clinical study	BC	Simvastatin 20 mg daily	–	15 female patients	–	5–38 days	Apoptosis ↓ proliferation↓ PTEN expression↑ phosphorylation of AKT at Ser473 and S6RP at Ser235/236↓	Wang et al. (2016)
Pathogen-free BALB/c nude mice (weighing 19 ± 2 g, SPF grade)	RCC	Simvastatin (5 mg/kg/d by oral gavage)	Normal saline (5 mg/kg/d by oral gavage	10	10	5 weeks	Apoptosis ↓ phosphorylation of AKT, ERK, and STAT3↓	Fang et al. (2013)
Female NMRI nu/nu mice	CRC	Simvastatin (50 mg/kg/day)	No treatment	8	8	3 weeks	Apoptosis↓ activation of PTEN, which is dependent on BMP signaling↑	Ouahoud et al. (2021b)
Seven weeks old male C57BL/6 mice	Myopathy	Simvastatin (5 mg/kg/day dissolved in water)	Water by oral gavage	8	8	3 weeks	Apoptosis ↓ PTEN expression↑ phosphorylation of AKT at Ser473 and S6RP at Ser235/236↓	Bonifacio et al. (2015)
Adult male Wistar rats	Burn wound	Simvastatin (5 mg dissolved in paraffin oil)	No treatment	50	10	2 weeks	Accelerated second-degree wound closure, prompted re-epithelialization, collagen deposition, and fibroblast to myofibroblast transdifferentiation angiogenesis↑ Akt, mTOR expression ↓	Ramhormozi et al. (2021)
60–90 days Male Swiss mice	Depression	Atorvastatin (0.1 mg/kg)	No treatment	–	–	–	Akt, mTOR expression ↓ GSK-3β signaling pathways↓ hippocampal immunocontent of phosphorylated Ser-473-Akt, Ser-9-GSK-3β and Ser-2481-mTOR proteins ↑	Ludka et al. (2017)
Female G93ASOD1 transgenic mice and age-matched wild type littermates	ALS	Simvastatin (20 mg/kg)	No treatment	18	18		Aggravated the autophagic flux impairment, enhanced muscle atrophy, fibrosis, muscle regeneration or myogenesis, mTOR + /eMHC + ↓	Kim and Kim (2018)

Table 1 (continued)

Study design	Disease	Intervention		Number of Patients		Treatment Duration	Results	Refs.
		Case	Control	Case	Control			
Male Wistar rats (8–10 w, 250–300 g)	Avascular necrosis of femoral head	Pravastatin (1 µM) 3-MA (5 mM)	No treatment	30	30	30 days	Autophagy↑ phosphorylation of AMPK, mTOR↓ apoptosis ↓	Liao et al. (2018)

CRC colorectal cancer, *RCC* renal cell carcinoma, *ALS* amyotrophic lateral sclerosis, *ERK* extracellular signal-regulated kinase, *PTEN* phosphatase and tensin, *STAT3* Signal Transducer and Activator of Transcription 3, *MYH* myosin heavy chain, *GSK-3β* Glycogen Synthase Kinase 3 Beta, *BC* breast cancer, *CRC* colorectal cancer

was decreased by lovastatin. Besides, the phosphorylation of AKT, (NF)-κB, and mTOR subsequently decreased (Xia et al. 2001; Zhu et al. 2019). Lovastatin in combination with temozolomide (TMZ), decreased the phosphorylation of AKT and the mTOR expression in both U87 and U251 cell lines when compared with TMZ alone. Moreover, lovastatin decreased LAMP2 and death in both U87 and U251 cell lines (Zhu et al. 2019). TMZ is a chemotherapeutic drug used in combination with radiotherapy to treat newly diagnosed GBM patients. Zhu et al. evaluated the effect of TMZ and lovastatin combination therapy in GBM cells. They found that lovastatin enhanced the cytotoxicity of TMZ and TMZ-induced apoptosis and impaired the autophagic flux of GBM cells. These authors claimed that impairment in autophagic flux following lovastatin administration could be explained by inhibition of autophagosome-lysosome fusion machinery and the AKT/mTOR pathway (Zhu et al. 2019).

The details of how statin-dependent activation of BMP might have an effect on CRC was recently explained by Jacobs et al. using Kinome-wide analysis. Lovastatin treatment was associated with dephosphorylation of mTOR, AKT, and 70S6K and, even more important, they suggested that the AKT/mTOR inhibition was dependent on the PTEN activity (Ouahoud et al. 2021).

Fluvastatin

Fluvastatin was shown to induce apoptosis and inhibit the proliferation of RCC cells in vitro (Table 2). Activation of AKT inhibits the downstream effects of mTOR and p70 S6 kinase (Cui et al. 2017). Fluvastatin blocks the mTOR phosphorylation and p70 S6 kinase. The inhibition of p70 S6 kinase motility by fluvastatin suggests that this statin might have antitumor effects (Okubo et al. 2020; Lindqvist and Pelletier 2009). The mechanisms behind statins-induced apoptosis, including fluvastatin, in HNSCC were explained by Tsubaki et al. (Tsubaki et al. 2017). It was shown that fluvastatin and simvastatin enhanced apoptosis by activating the caspase-3 (a key indicator of cell apoptosis), and inhibiting the geranylgeranyl pyrophosphate (GGPP). GGPP is a major substrate for anchoring Ras to the membrane. Decrease of GGPP is associated with dissociation of Ras from the membrane and consequently inhibiting the Ras-mediated growth signaling (McTaggart 2006; Schubbert et al. 2007). These authors demonstrated that suppression of the membrane localization of Ras and up-regulation of Bim contributed to inhibition of the ERK and mTOR signaling pathways.

Pravastatin

Pravastatin induces autophagy in endothelial cells in vivo and in vitro (Table 1) (Nakao et al. 2007). 3-MA, as

Table 2 In vitro studies on mTOR/statins interaction in inflammatory diseases

Study design	Disease	Intervention		Number of cells		Treatment duration	Results	Refs.
		Case	Control	Case	Control			
In vitro 786–0 and CAKI-2 cell lines	RCC	Fluvastatin (5 μmol/L)	DMSO	–	–	–	Apoptosis ↓ proliferation↓ PTEN expression↑ phosphorylation of AKT, p70 S6 kinase ↓ formation of 4E-BP1-eIF4E complexes↑ up-regulation of PDCD4↑	Woodard et al. (2008)
In vitro A498 and 786-O cell lines	RCC	simvastatin (8 and 16 μM)	–	A498 (2×10^3 cells/well) and 786-O (1×10^3 cells/well)	–	–	Apoptosis ↓ proliferation↓ PTEN expression↑ phosphorylation of AKT, ERK, IL-6/JAK2/STAT3↓	Fang et al. (2013)
In vitro HSC-3, HEp-2, Ca9-22, and SAS cell lines	HNSCC	HSC-3, Ca9-22, and SAS cells were treated with 1 μM fluvastatin or 2.5 μM simvastatin and HEp-2 cells were treated with 20 μM fluvastatin or 40 μM simvastatin	0.1% DMSO	2×10^3 cells/well	–	–	Apoptosis ↓ phosphorylation of AKT, ERK ↓ Suppression of membrane localization of Ras and up-regulation of Bim, suppression of GGPP formation	Tsubaki et al. (2017)
In vitro ECC-1 and Ishikaw cell lines	EC	Simvastatin (1, 10, and 25 μM)	DMSO	4×10^3 cells/well	–		Apoptosis ↓ phosphorylation of MAPK pathway ↓	Schointuch et al. (2014)
In vitro *TSC2*-null and LAM-derived cells cell lines	AM	Simvastatin and atorvastatin (0.5, 1.0, 5.0, and 10 μM)	Diluent	1.5×10^5 cells/well	–	6 days	Apoptosis ↓ proliferation↓ phosphorylation of AKT, ERK ↓	Atochina-Vasserman et al. (2013)
In vitro MCF-7 (ER +), T47D (ER +), MDA-MB-231 (ER-) and BT-549 (ER-) cell lines	BC	MCF-7 and T47D were treated with 5, 10, and 20 μM simvastatin, MDA-MB-231 with 0.2, 04, 0.8 μM simvastatin, BT-549 with 2.5, 5, 10 μM simvastatin	DMSO	–	–	–	Apoptosis ↓ proliferation↓ PTEN expression↑ phosphorylation of AKT, ERK, MAPK ↓	Wang et al. (2016)

Table 2 (continued)

Study design	Disease	Intervention		Number of cells		Treatment duration	Results	Refs.
		Case	Control	Case	Control			
In vitro LNCaP, 22RV1, PC3, DU145, and RWPE-1 cell lines	PCa	5 mM metformin and 10 μM simvastatin	–	3–5 × 10^3 cells/well	–	For 24, 48, and 72 h	Proliferation↓ phosphorylation of AKT, ERK, mTOR, MKI67 and IGF1R ↓	Jiménez-Vacas et al. (2021)
In vitro U87 and U251 cell lines	GBM	Lovastatin (5 μM)	–	4 × 10^3 cells/well	–	For 72 h	Autophagy↑ phosphorylation of AKT, ERK ↓	Zhu et al. (2019)
In vitro HCT116, RKO and HT29 cell lines	CRC	Lovastatin (2 μM)	–	–	–	–	Apoptosis ↓ PTEN expression↓	Ouahoud et al. (2021)
In vitro C2C12 myoblasts cell line	Myopathy	10 or 50 μM simvastatin, rosuvastatin, atorvastatin	0.1% DMSO	1.5 × 10^4 cells/well	–	24 h	Apoptosis ↓ PTEN expression↑ phosphorylation of AKT, p70 S6 kinase ↓	Bonifacio et al. (2015)
In vitro SH-SY5Y cell line	Parkinson	Rosuvastatin (10. 20, and 40 μM)	–	5 × 10^4 cells/well	–	–	Autophagy↑ phosphorylation of AMPK, Beclin-1, mTOR, LAMP-2↓	Kang et al. (2017)
In vitro lung cancer cells	Lung cancer cells	pitavastatin at 0.5, 2 and 8 μM	–	100 μl of 10 million cells	–	72 h	Apoptosis ↓ proliferation↓	Hu et al. (2020)

CRC colorectal cancer, *RCC* renal cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *EC* endometrial cancer, *LAM* lymphangioleiomyomatosis, *BC* breast cancer, *PCa* prostate cancer, *GBM* glioblastoma multiform, *ERK* extracellular signal-regulated kinase, *PTEN* phosphatase and tensin, *4E-BP1-eIF4E* Eukaryotic initiation factor 4E- binding protein 1, *PDCD4* Programmed Cell Death 4, *STAT3* Signal Transducer and Activator of Transcription 3, *JAK2* Janus kinase 2, *GGPP* Geranylgeranyl Pyrophosphate, *MAPK* mitogen-activated protein kinase, *PKB* protein kinase B, *IGF1R* Insulin-like growth factor 1 receptor, *LAMP2* Lysosomal Associated Membrane Protein 2, *BNP* bone morphogenetic protein

an autophagy inhibitor, decreased pravastatin-induced autophagy (Liao et al. 2018). It has been shown that pravastatin downregulated the AMPK/mTOR signaling pathway, thus blocking the inflammatory process (Emanueli et al. 2007). Pravastatin was shown to protect endothelial cells from dexamethasone-induced autophagy by inhibition of the AMPK-mTOR signaling pathway (Nakao et al. 2007).

Rosuvastatin

Downregulation of the mTOR expression, upregulation of Beclin-1 expression, and the activation of autophagic system were found to be beneficial in PD (Table 2). Rosuvastatin was shown to decrease the mTOR levels and increase the Beclin-1 levels in patients with PD (Kang et al. 2017).

Pitavastatin

It was found that pitavastatin inhibited the PI3K/Akt/mTOR signaling which led to a decrease in apoptosis and cell proliferation (Table 2) (Hu et al. 2020; Tajiri et al. 2014).

Conclusion

Statins are currently the most often prescribed and effective LDL-C lowering drugs for prevention of atherosclerotic CVD. Statins decrease total and LDL-C, reduce triglycerides, and slightly increase HDL-cholesterol. Therefore, they are decreasing the risk of cardiovascular events and cardiovascular mortality. In addition to cholesterol metabolism, statins also participate in decreasing the circulating isoprenoids, and inactivation of signaling proteins. Statins also have anti-inflammatory, antioxidant, antiproliferative and immunomodulatory effects (Bahrami et al. 2018; Parizadeh et al. 2011; Koushki et al. 2021). Statins can stabilize atherosclerotic plaques and prevent platelet aggregation as well (Kim et al. 2019; Chidambaram et al. 2021). Statins are generally very well tolerated drugs. However, like all pharmaceuticals, they have adverse effects. Adverse effects of statins may affect muscles, and to a much less extent liver. Patients who are treated with statins, particularly with high doses, have an increased rate of myopathies and extremely rarely rhabdomyolysis. All these adverse effects are rare, and the safety of statins is generally very acceptable (Kim and Choi 2021; Adhyaru and Jacobson 2018). Many studies have shown that the mTOR signaling pathway is effective in initiating inflammation and inflammation and diseases. Activation of the mTOR/ NF-kB pathway results in upregulation of the IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, and TNF-α. On the other hand, induction of the P13K/AKT/mTOR pathway promotes the TNF-α, IL-1β, TGF-β, IL-12, and IL-6 secretion (Lashgari et al. 2020). The conclusion of this extensive literature review might be that many statins are able to downregulate the mTOR signaling pathway and modulate the cell hemostasis and autophagy. Both the mTORC1 and mTORC2 signaling pathways are blocked by statins in adipose tissue (Martinet et al. 2014). Inhibition of the mTOR signaling pathway by statins may be a target for treatment of different inflammatory and maybe also some malignant (as an adjunct treatment) diseases.

Data availability There is no raw data associated with this review article.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

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